

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Heikki HYOTY, et al  
Application No.: 10/009,016 Group No.: 1645  
Filed: March 12, 2002 Examiner: Mary Mosher  
For: PREVENTION OF TYPE 1 DIABETES AND OTHER NON-POLIO  
ENTEROVIRUS DISEASES

Attorney Docket No.: U 013757-2

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

INFORMATION DISCLOSURE STATEMENT

Applicants call the Examiner's attention to the attached publications which show (a) the connection between enterovirus infections and type 1 diabetes (see

---

**CERTIFICATION UNDER 37 C.F.R. 1.8(a) and 1.10\***  
(When using Express Mail, the Express Mail label number is mandatory.  
Express Mail certification is optional.)

I hereby certify that, on the date shown below, this correspondence is being:

MAILING

deposited with the United States Postal Service in an envelope addressed to the Commissioner for Patents, P. O. Box 1450, Alexandria, VA 22313-1450.

37 C.F.R. 1.8(a)

37 C.F.R. 1.10\*

with sufficient postage as first class mail.

as "Express Mail Post Office to Address"  
Mailing Label No. \_\_\_\_\_ (mandatory)

TRANSMISSION

transmitted by facsimile to the Patent and Trademark Office, to (708) 872-9306

Date: January 5, 2005

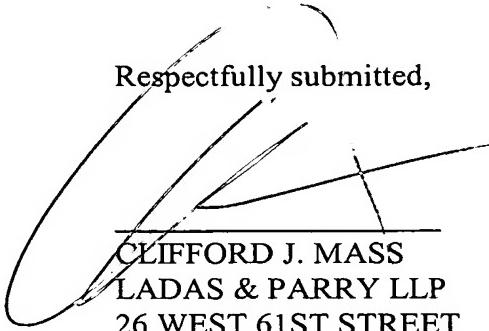
Signature

CLIFFORD J. MASS  
(type or print name of person certifying)

\*WARNING: Each paper or fee filed by "Express Mail" must have the number of the "Express Mail" mailing label placed thereon prior to mailing. 37 C.F.R. 1.10(b).  
"Since the filing of correspondence under § 1.10 without the Express Mail mailing label thereon is an oversight that can be avoided by the exercise of reasonable care, requests for waiver of this requirement will not be granted on petition." Notice of Oct. 24, 1996, 60 Fed. Reg. 56,439, at 56,442.

references BA - BW); and/or (b) the presence of enterovirus in the pancreatic islets in diabetic or prediabetic subjects (see references AP - AU). PTO Form 1449 is attached with reference copies.

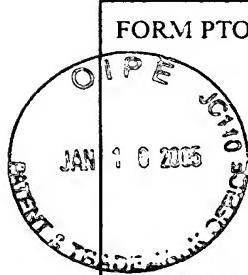
Respectfully submitted,

  
CLIFFORD J. MASS  
LADAS & PARRY LLP  
26 WEST 61ST STREET  
NEW YORK, NEW YORK 10023  
REG. NO.30,086(212)708-1890

FORM PTO-1449 JAN 10 2005 U.S. PATENT AND TRADEMARK OFFICE		U. S DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE		ATTY. DOCKET NO.	SERIAL NO.	
				<b>U 013757-2</b>	<b>10/009,016</b>	
				<b>APPLICANT</b>		
				<b>Heikki HYOTY, et al</b>		
				FILING DATE	GROUP	
				<b>March 12, 2002</b>	<b>1645</b>	
<b>U.S. PATENT DOCUMENTS</b>						
EXAMINER INITIALS	REFERENCE DESIGNATION	DOCUMENT NUMBER	DATE	NAME	FILING DATE IF APPROPRIATE	
	AA					
	AB					
	AC					
	AD					
	AE					
<b>FOREIGN PATENT DOCUMENTS</b>						
		DOCUMENT NUMBER	DATE	COUNTRY	TRANSLATION	
					YES	NO
	AL					
	AM					
	AN					
	AO					
<b>OTHER ART (Including Author, Title, Date, Pertinent Dates, Etc.)</b>						
	AP	Screening of organ donors for anti-islets antibodies and characterization of pancreatic histology in an antibody positive subject. Giannani, Dotta, Di Mario, Scipioni, Grassetti, Liggins, Yu, Eisenbarth. Immunology of Diabetes Society Conference. Cambridge England March 28-31 2004				
	AQ	Human Beta-Cell Specific Enteroviral Infection Impairs insulin secretion and upregulates islet chemokine and fas expression. Grassetti, Scipioni, Del Guerra, Lettieri, Sbrana, Mario, Marchetti, Dotta. Immunology of diabetes society conference. Cambridge England March 28-31 2004				
	AR	Demonstration of enterovirus infection in islets of two patients with type 1 diabetes. Dotta, Santangelo, Marselli, Dionisi, Scipioni, Masini, van Halteren, Del Prato, Di Mario, Roep, Marchetti. Diabetes/Metabolism Research and Reviews. November-December 2002				
	AS	Enterovirus infection in human pancreatic islet cells, islet tropism in vivo and receptor involvement in cultured islet beta cells. Ylipaasto, Klingel, Lindberg, Otonkoski, Kandolf, Hovi, Riovainen. Diabetologia (2004)				
	AT	Virus-induced diabetes mellitus. Yoon, Austin, Onodera, Notkins. Vol. 300 NO. 21 Laboratory of Oral Medicine.				
	AU	Human beta cell specific enteroviral infection induces pro-apoptotic changes as evidenced by microarray gene expression profiling. Grassetti, Scipioni, Lupi, Del Prato, Marchetti, Dotta. Diabetologia Volume 47 , article 488 page A179				
EXAMINER			DATE CONSIDERED			
EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.						

FORM PTO-1449		U. S DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE		ATTY. DOCKET NO.	SERIAL NO.
				U 013757-2	10/009,016
				APPLICANT	
				Heikki HYOTY, et al	
				FILING DATE	GROUP
				March 12, 2002	1645
U.S. PATENT DOCUMENTS					
EXAMINER INITIALS	REFERENCE DESIGNATION	DOCUMENT NUMBER	DATE	NAME	FILING DATE IF APPROPRIATE
	AA				
	AB				
FOREIGN PATENT DOCUMENTS					
		DOCUMENT NUMBER	DATE	COUNTRY	TRANSLATION
					YES
	AL				
OTHER ART (Including Author, Title, Date, Pertinent Dates, Etc.)					
	BA	Enterovirus-related type 1 diabetes mellitus and antibodies to glutamic acid decarboxylase in Japan. Kawashima, Ihara, Loi, Oana, Sato, Kato, Takami, Kashiwagi, Takekuma, Hoshika, Mori. Journal of Infection, August 2004 49(2): 147-51			
	BB	Simultaneous Onset of Type 1 Diabetes Mellitus in Identical Infant Twins with Enterovirus Infection. Smith, Clements, Riding, Collins, Bottazzo, Taylor. Diabetic Medicine 1998 15: 515-517			
	BC	Enterovirus RNA is found in Peripheral Blood Mononuclear Cells in a Majority of Type 1 Diabetic Children at Onset. Yin, Berg, Tuvemo, Frisk. Diabetes, Vol 51, June 2002			
	BD	Reduced Frequency of HLA DRB1*03-DQB1*02 in Children with Type 1 Diabetes Associated with Enterovirus RNA. Craig, Howard, Silink, Rawlinson. Journal of Infectious Diseases May 15, 2003			
	BE	Enterovirus Variants in the serum of children at the onset of Type 1 diabetes mellitus. Nairn, Galbraith, Taylor, Clements. British Diabetic Association, Diabetic Medicine 16, 509-513 1999			
	BF	Coxsackie B Virus infection and onset of childhood diabetes. Clements, Galbraith, Taylor. The Lancet, Vol 346, July 22, 1995 pgs 221-223			
	BG	Detection of Coxsackie B Virus RNA Sequences in Whole Blood Samples from adult patients at the onset not Type 1 diabetes mellitus. Andreoletti, Hober, Hober-Vandenbergh, Belaich, Vantyghem, Lefebvre, Wattre,. Juornal of Medical Vriology 52:121-127 (1997)			
	BI	Neonatal Type 1 diabetes associated with maternal echovirus 6 infection: a case report. Otonkoski, Roivainen, Vaarala, Dinesen, Leipala, Hovi, Knip. Diabetologia (2000) 43: 1235-1238			
	BJ	Serologic Evidence of an Association between Enteroviruses and the onset of Type 1 diabetes mellitus. Helfand, Gary, Jr., Freeman, Anderson, Pallansch. The Journal of Infectious Diseases 1995: 172-1206-11			
	BK	Increased level of interferon- $\alpha$ in blood of patients with insulin-dependent diabetes mellitus: Relationship with coxsackievirus B infection. Chehadeh, Weill, Vantyghem, Alm, Lefebvre, Wattre, Hober. The Journal of Infectious Diseases 2000; 181:1929-39			
EXAMINER			DATE CONSIDERED		
EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.					

 <b>FORM PTO-1449</b> <b>U. S DEPARTMENT OF COMMERCE</b> <b>PATENT AND TRADEMARK</b> <b>OFFICE</b>  <b>INFORMATION DISCLOSURE</b> <b>STATEMENT BY APPLICANT</b>  (Use several sheets if necessary)		<b>ATTY. DOCKET NO.</b>		<b>SERIAL NO.</b>	
		<b>U 013757-2</b>		<b>10/009,016</b>	
		<b>APPLICANT</b>			
		<b>Heikki HYOTY, et al</b>			
		<b>FILING DATE</b>		<b>GROUP</b>	
		<b>March 12, 2002</b>		<b>1645</b>	
<b>U.S. PATENT DOCUMENTS</b>					
<b>EXAMINER INITIALS</b>	<b>REFERENCE DESIGNATION</b>	<b>DOCUMENT NUMBER</b>	<b>DATE</b>	<b>NAME</b>	<b>FILING DATE IF APPROPRIATE</b>
	AA				
	AB				
	AC				
<b>FOREIGN PATENT DOCUMENTS</b>					
		<b>DOCUMENT NUMBER</b>	<b>DATE</b>	<b>COUNTRY</b>	<b>TRANSLATION</b>
					<b>YES</b>
	AL				
	AM				
<b>OTHER ART</b> (Including Author, Title, Date, Pertinent Dates, Etc.)					
	BL	Characterization of the T-Cell response to Coxsackievirus B4. Evidence that effector memory cells predominate in patients with Type 1 diabetes. Varela-Calvino, Ellis, Sgarbi, Dayan, Peakman. Diabetes, vol. 51, June 2002			
	BM	Prediction and prevention of Type 1 diabetes mellitus. PS 30., Schlosser, Mentel Moya-Suri, Wassmuth, Gurtler, Moritz, Greifswald, Arndt. Diabetologia, vol 47 supplement 1, A 183			
	BN	Enterovirus infections are associated with the induction of β-Cell autoimmunity in a prospective birth cohort study. Salminen, Sadeharju, Lonnrot, Vahasalo, Kupila, Korhonen, Ilonen, Simell, Knip, Hyoty. Journal of Medical Virology 69:91-98 (2003)			
	BO	Enterovirus infections as a risk factor for type I diabetes: virus analyses in a dietary intervention trial. Sadehaju, Hamalainen, Knip, Lonnrot, Koskela, Virtanen, Ilonen, Akerblom, Hyoty. Clin. Exp. Immunol 2003; 132: 271-277			
	BP	Enterovirus antibody levels during the first two years of life in prediabetic autoantibody-positive children. Sadeharju, Lonnrot, Kimpinaki, Savola, Erkkila, Kalliokoski, Savolainen, koskela, Ilonen, Simell, Knip, Hyoty. Diabetologia (2001) 44: 818-823			
	BQ	Enterovirus RNA in Serum is a risk factor for beta-cell autommunity and clinical Type 1 diabetes: A prospective study. Lonnrot, Salminen, Knip, Savola, Kulmala, Leinikki, Hyypia, Akerblom, Hyoty. Juornal of Medical Virology 61:214-220 (2000)			
	BR	T-Cell responses to enterovirus antigens in children with Type 1 diabetes. Juhela, Hyoty, Roivainen, Harkonen, Putto-Laurila, Simell, Ilonen. Diabetes, vol. 49, August 2000 pgs 1308-1313			
	BS	Islet cell antibody seroconversion in children is temporally associated with enterovirus infections. Hiltunen, Hyoty, Knip, Ilonen, Reijonen, Vahasalo, Roivainen, Lonnrot, Leinikki, Hovi, Akerblom. The Journal of Infectious Diseases 1997; 175:554-60			
	BT	A prospective study of the role of coxsackie B and other enterovirus infections in the pathogenesis of IDDM. Hyoty, Hitunen, Knip, Laakkonen, Vahasalo, Karjalainen, Koskela, Roivainen, Leinikki, Hovi, Akerblom. Diabetes, vol. 44, June 1995 pgs 652-657			
<b>EXAMINER</b>			<b>DATE CONSIDERED</b>		
EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.					



FORM PTO-1449	U. S DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	ATTY. DOCKET NO.	SERIAL NO.
		U 013757-2	10/009,016
		APPLICANT	
		Heikki HYOTY, et al	
		FILING DATE	GROUP
		March 12, 2002	1645

## U.S. PATENT DOCUMENTS

EXAMINER INITIALS	REFERENCE DESIGNATION	DOCUMENT NUMBER	DATE	NAME	FILING DATE IF APPROPRIATE
	AA				
	AB				
	AC				
	AD				
	AE				
	AF				
	AG				
	AH				

## FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	DATE	COUNTRY	TRANSLATION	
					YES	NO
	AL					
	AM					
	AN					
	AO					
	AP					

## OTHER ART (Including Author, Title, Date, Pertinent Dates, Etc.)

BU	Detection of enterovirus RNA sequences in serum samples from autoantibody-positive subjects at risk for diabetes. Coutant, Palmer, Carel, Cantero-Aguilar, Lebon, Bougnères. 2002 Diabetes UK Diabetic Medicine, 19 966-971.
BV	Echovirus 4 and Type 1 diabetes mellitus. Diaz-Horta, Bello, Cabrera-Rode, Suarez, mas, Garcia, Abalos, Jofra, Molina, Diaz-Diaz, Di Mario. Autoimmunity Vol. 34 pp. 275-281
BW	Type 1 diabetes islet associated antibodies in subjects infected by echovirus 16. Cabrera-Rode, Sarmiento, Tiberti, Molina, Barrios, Hernandez, Diaz-Horta, Di Mario. Diabetologia (2003) 46: 1348-1353.

EXAMINER	DATE CONSIDERED
EXAMINER:	Initial if citation considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.



Practitioner's Docket No. U 013757-2

1845  
PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Heikki HYOTY, et al  
Application No.: 10/009,016 Group No.: 1645  
Filed: March 12, 2002 Examiner: Mary Mosher  
For: PREVENTION OF TYPE 1 DIABETES AND OTHER NON-POLIO ENTEROVIRUS  
DISEASES

Commissioner for Patents  
P. O. Box 1450  
Alexandria, VA 22313-1450

TRANSMITTAL OF INFORMATION DISCLOSURE STATEMENT  
BEFORE MAILING DATE OF EITHER A FINAL ACTION  
OR NOTICE OF ALLOWANCE (37 C.F.R. 1.97(c))

NOTE: 37 C.F.R. 1.97: "(c) An information disclosure statement shall be considered by the Office if filed after the period specified in paragraph (b) of this section, provided that the information disclosure statement is filed before the mailing date of any of a final action under § 1.113, a notice of allowance under § 1.311, or an action that otherwise closes prosecution in the application, and it is accompanied by one of:

- (1) The statement specified in paragraph (e) of this section; or
- (2) The fee set forth in § 1.17(p)."

NOTE: "If a final action or notice of allowance is mailed in an application and later withdrawn, the application will be considered as not having had a final action or notice of allowance mailed for purposes of considering an information disclosure statement." Notice of April 20, 1992 (1138 O.G. 37-41, 39).

---

CERTIFICATION UNDER 37 C.F.R. 1.8(a) and 1.10\*  
(When using Express Mail, the Express Mail label number is mandatory;  
Express Mail certification is optional.)

I hereby certify that, on the date shown below, this correspondence is being:

MAILING

- deposited with the United States Postal Service in an envelope addressed to the Commissioner for Patents , P. O. Box 1450, Alexandria, VA 22313-1450.

37 C.F.R. 1.8(a)

37 C.F.R. 1.10\* (Preferred)

- with sufficient postage as first class mail.  as "Express Mail Post Office to Address" Mailing Label No. \_\_\_\_\_ (mandatory)

TRANSMISSION

- transmitted by facsimile to the Patent and Trademark Office. to (703) 872-9306

Date: January 5, 2005

Signature

CLIFFORD J. MASS  
(type or print name of person certifying)

\* Only the date of filing (§ 1.6) will be the date used in a patent term adjustment calculation, although the date on any certificate of mailing or transmission under § 1.8 continues to be taken into account in determining timeliness. See § 1.703(j). Consider "Express Mail Post Office to Addressee" (§ 1.10) or facsimile transmission (§ 1.6(d)) for the reply to be accorded the earliest possible filing date for patent term adjustment calculations.

**NOTE:** 37 C.F.R. § 1.704(d): "A paper containing only an information disclosure statement in compliance with §§ 1.97 and 1.98 will not be considered a failure to engage in reasonable efforts to conclude prosecution (processing or examination) of the application under paragraphs (c)(6), (c)(8), (c)(9), or (c)(10) of this section if it is accompanied by a statement that each item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart application and that this communication was not received by any individual designated in § 1.56(c) more than thirty days prior to the filing of the information disclosure statement. This thirty-day period is not extendable."

**NOTE:** "If information submitted during the period set forth in 37 C.F.R. 1.97(c) with a certification is used in a new ground of rejection on unamended claims, the next Office action will not be made final since in this situation it is clear that applicant has submitted the information to the office promptly after it has become known and the information is being submitted prior to a final determination on patentability by the Office. However, the information submitted with a certification can be used in a new ground of rejection and the next Office action made final, [i]f the new ground of rejection was necessitated by amendment of the application by applicant. Where the information is submitted during this period with a fee, the examiner may use the information submitted, e.g., printed publication or evidence of public use, and make the next Office action final whether or not the claims have been amended, provided that no other new ground of rejection which was not necessitated by amendment to the claims is introduced by the examiner. See MPEP 706.07(a). If a new ground of rejection is introduced that is neither necessitated by an amendment to the claims nor based on the information submitted with the fee set forth in 37 C.F.R. 1.17(p), the Office action shall not be made final. Notice of April 20, 1992 (1138 O.G. 37-41, 39).

**WARNING:** "A petition for suspension of action to allow applicant time to submit an information disclosure statement will be denied as failing to present good and sufficient reasons, since 37 C.F.R. 1.97 provides adequate recourse for the timely submission of prior art for consideration by the examiner." Notice of July 6, 1992 (1141 O.G. 63). But see § 103(b) and (c), limited suspension of action in a continued prosecution application (CPA) filed under § 1.53(d) and in a request for continued examination (RCE) under § 1.114.

**WARNING:** No extension of time can be had under 37 C.F.R. 1.136(a) or (b) for filing an IDS. 37 C.F.R. 1.97(f).

#### **TIME OF TRANSMITTAL OF ACCOMPANYING INFORMATION DISCLOSURE STATEMENT**

1. The information disclosure statement transmitted herewith is being filed *after* three months of the filing date of this national application or the date of entry of the national stage as set forth in § 1.491 in an international application or after the mailing date of the first Office action on the merits, whichever event occurred last but *before* the mailing date of either:

- (1) a final action under § 1.113 or
- (2) a notice of allowance under § 1.311,

whichever occurs first.

#### **STATEMENT OR FEE**

2. Accompanying this transmittal is

(check either A or B below)

- A.  a statement as specified in 37 C.F.R. 1.97(e).

**OR**

- B.  the fee set forth in 37 C.F.R. 1.17(p) for submission of an information disclosure statement under § 1.97(c). (\$180.00).

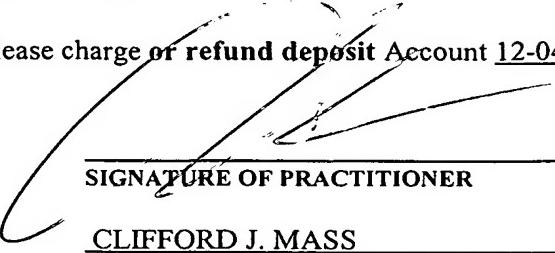
#### **METHOD OF PAYMENT OF FEE**

3.

- Attached is a check in the amount of \$ 180.  
 Charge Account No.        in the amount of \$       .  
A duplicate of this request is attached.

If any additional **or lesser** fees are due, please charge **or refund deposit** Account 12-0425.

Reg. No. 30086

  
SIGNATURE OF PRACTITIONER

Tel. No.: (212) 708-1890

CLIFFORD J. MASS

(type or print name of practitioner)

Customer No.: 00140

P.O. Address

c/o Ladas & Parry LLP  
26 West 61<sup>st</sup> Street  
New York, N.Y. 10023



PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Heikki HYOTY, et al  
Application No.: 10/009,016 Group No.: 1645  
Filed: March 12, 2002 Examiner: Mary Mosher  
For: PREVENTION OF TYPE 1 DIABETES AND OTHER NON-POLIO  
ENTEROVIRUS DISEASES

Attorney Docket No.: U 013757-2

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

SUPPLEMENTAL RESPONSE

Further to Applicants' Amendment dated 15 November 2004, and in  
supplemental response to the Official Action of 15 June 2004, Applicants submit

---

**CERTIFICATION UNDER 37 C.F.R. 1.8(a) and 1.10\***  
(When using Express Mail, the Express Mail label number is mandatory;  
Express Mail certification is optional.)

I hereby certify that, on the date shown below, this correspondence is being:

MAILING

- deposited with the United States Postal Service in an envelope addressed to the Commissioner for Patents, P. O. Box 1450, Alexandria, VA 22313-1450.

37 C.F.R. 1.8(a)

37 C.F.R. 1.10\*

- with sufficient postage as first class mail.

as "Express Mail Post Office to Address"  
Mailing Label No. \_\_\_\_\_ (mandatory)

TRANSMISSION

- transmitted by facsimile to the Patent and Trademark Office, to (708) 872-9306

Date: January 5, 2005

Signature

CLIFFORD J. MASS

(type or print name of person certifying)

\*WARNING: Each paper or fee filed by "Express Mail" must have the number of the "Express Mail" mailing label placed thereon prior to mailing. 37 C.F.R. 1.10(b).  
"Since the filing of correspondence under § 1.10 without the Express Mail mailing label thereon is an oversight that can be avoided by the exercise of reasonable care, requests for waiver of this requirement will not be granted on petition." Notice of Oct. 24, 1996, 60 Fed. Reg. 56,439, at 56,442.

herewith copies of publications which substantiate the remarks in Applicants' aforementioned Amendment regarding the recent studies which have been carried out that demonstrate the connection between enterovirus infections and type 1 diabetes (see Amendment dated 15 November 2004 at page 13, first paragraph). The studies include studies published by the group of the inventors and studies demonstrating the presence of enterovirus in the pancreatic islets in diabetic or prediabetic subjects.

An Information Disclosure Statement including citation of the aforementioned publications is also submitted herewith.

An early and favorable reconsideration of the application in view of the present submission is again respectfully requested.

Respectfully submitted,

CLIFFORD J. MASS  
LADAS & PARRY LLP  
26 WEST 61ST STREET  
NEW YORK, NEW YORK 10023  
REG. NO.30,086(212)708-1890